REMARKS

Status of the Claims

Claims 22-24 are pending in this application with claim 22 being the sole independent claim.

Claim Rejections Under 35 U.S.C. § 103

Johnson, Saito and Baylor

Claims 22 and 24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson *et al.* ("Johnson"), Saito *et al.*, U.S. 2005/0158330 ("Saito"), and Baylor *et al.* (2002) *Vaccine 20*:S18-S23 ("Baylor"). (Office Action, page 3). Applicants respectfully traverse this rejection for the reasons set fort in the previous response (*see* After-Final Amendment and Reply filed June 19, 2008, pages 4-7). Below, Applicants present additional remarks regarding this rejection.

The present invention is a non-obvious advance over the prior art in that it combines a defined oil emulsion adjuvant with aluminum hydroxide in a vaccine composition against *E. coli* O157:H7. The unexpected advantages of combining an oil emulsion adjuvant as defined by the present claims with aluminum hydroxide are detailed in the Declaration of Wumin Li, filed on July 9, 2007 ("the Li Declaration"). The Li Declaration shows that an inactivated *E. coli* O157:H7 vaccine adjuvanated with SP oil (an oil emulsion within the scope of the present claims) plus aluminum hydroxide produced a markedly enhanced immune response in calves, as compared to a vaccine composition containing aluminum hydroxide only.

Applicants maintain that it would have been highly unlikely, if not impossible, for a person of ordinary skill in the art to reconstruct the oil emulsion of the present claims based on the multiple laundry lists of ingredients presented in Saito. In addition, and most significant for the purposes of the present response, none of the cited references teach or suggest combining an oil emulsion adjuvant with aluminum hydroxide.

In the present Office Action, it is stated that "Saito et al. disclose using aluminum hydroxide in the disclosed composition." The Examiner cited to paragraphs [0101] and [0109] of Saito to support this assertion. (*See* Office Action, page 5). Applicants respectfully submit that this is an incorrect interpretation of Saito. In particular, Saito only mentions aluminum hydroxide in the

context of being used by itself in comparative control vaccine compositions. The focus of Saito is on a water-in-oil-in-water ("W/O/W") emulsion adjuvant. (*See* Saito Abstract, first sentence). Saito never states or suggests that aluminum hydroxide could or should be included in the W/O/W emulsion adjuvant.

For example, in paragraph [0101], Saito refers to vaccine compositions containing inactivated *Erysipelothrix rhusiopathiae* ("Er"). The test vaccines designated 1, 3, 5, 7, 10, 12 and 14 contain the W/O/W emulsions but do not contain aluminum hydroxide. Three control vaccine compositions are also mentioned in this paragraph: one containing Freund's incomplete adjuvant (IFA), one containing IFA and PEG (IFA-PEG), and one containing aluminum hydroxide. These controls are separate and distinct vaccine compositions that do not contain the W/O/W emulsion. (*See also* Saito, pages 8-9, Tables 6 and 7, wherein the results for "IFA," "IFA-PEG," and "aluminum gel" are listed separately from the experimental vaccines.)

Likewise, in paragraph [0109] Saito refers to comparative control vaccine compositions against *Mycoplasma hyopneumoniae* containing just aluminum hydroxide gel or just aluminum hydroxide gel plus PEG (designated "AL" and "AL-PEG," respectively). Again, the aluminum hydroxide is not added to the W/O/W emulsion formulations.

Thus, aluminum hydroxide is disclosed in Saito solely as a comparative control adjuvant. There is nothing to suggest combining aluminum hydroxide with the W/O/W emulsions.

In fact, the experimental results of Saito would have discouraged a person of ordinary skill in the art from using aluminum hydroxide in an oil emulsion vaccine composition. For example, Table 6 of Saito compares the "effectiveness" of the various Er vaccine formulations (expressed in terms of PD_{50}) with one another. The aluminum gel-adjuvanated formulation produced a miniscule PD_{50} of 77.1, whereas the experimental (oil emulsion) vaccine formulations produced PD_{50} values as high as 2660.1 (see "Vaccine 1"). Similarly, in the *Mycoplasma* experiments summarized in Table 8, the aluminum hydroxide-adjuvanated formulations performed much worse than the W/O/W formulations as measured by lesion score and percent decrease in lesions. According to Saito, "the aluminum gel vaccine did not at all show a lesion-decreasing effect by the vaccine, irrespective of the presence or otherwise of PEG addition." (*See* paragraph [0112], last sentence, emphasis added.) A skilled person having knowledge of the dismal performance of aluminum hydroxide gel as an adjuvant, as reported in Saito, would have

been highly discouraged from using aluminum hydroxide in combination with an oil emulsion vaccine formulation.

Baylor reinforces this conclusion. First, Baylor refers only to the use of aluminum hydroxide by itself. There is no suggestion to combine aluminum hydroxide with any other adjuvant system, much less an oil emulsion adjuvant. Second, Baylor emphasizes several negative aspects of aluminum hydroxide as an adjuvant including "local reactions, production of IgE antibodies, and the inability to elicit cell-mediated immunity." (*See* Baylor, page S22, left column). Baylor also indicates that aluminum hydroxide may not have effective adjuvant properties for certain kinds of vaccines. (*See* Baylor, page S22, left column: "not all vaccines have an enhanced antigenicity when adsorbed to aluminum.") In view of these negative attributes reported by Baylor, a person of ordinary skill in the art would have had serious misgivings about using aluminum hydroxide as an adjuvant for an *E. coli* O157:H7 vaccine. When the statements of Baylor are considered in conjunction with the results of Saito, a skilled person would have most certainly avoided adding aluminum hydroxide to an oil emulsion vaccine formulation.

As a final point, Applicants note that the Examiner has previously considered the Li Declaration but found it insufficient to overcome the obviousness rejection on the alleged basis that "the facts presented are not germane to the rejection and are not commensurate in scope with the claims." (*See* Office Action dated September 18, 2007, page 14). At that time, however, the claims simply recited "a metabolizable oil adjuvant" and did not specify aluminum hydroxide. Now, the currently presented claims recite the particular components of SP oil (the adjuvant specifically used in the experiments of the Li Declaration), along with aluminum hydroxide. Thus, the original basis for discounting the Li Declaration cannot apply with regard to the present claims. When reconsidered in light of the present claims and the discussion set forth above, Applicants are confident that the Examiner will find the Li Declaration more than sufficient to overcome the present obviousness rejections.

In view of the foregoing, Applicants respectfully request that the rejection of claims 22 and 24 based on Johnson, Saito and Baylor be reconsidered and withdrawn.

Johnson, Saito, Baylor and Elder

Claims 22-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson, in view of Saito and Baylor, and further in view of Elder *et al.* (2002) *J. Animal Sci. 80*:151,

abstract 602 ("Elder"). (Office Action, page 8). Applicants respectfully traverse this rejection for the reasons set forth immediately above and in Applicants' previous response. Elder does not cure any of the noted deficiencies of Johnson, Saito and/or Baylor.

In view of the foregoing, Applicants respectfully request that the rejection of claims 22-24 based on Johnson, Saito, Baylor and Elder be reconsidered and withdrawn.

Conclusion

Applicants believe that a full and complete response has been made to the outstanding Office Action. In view of the foregoing remarks, Applicants believe that this application is in condition for allowance, and prompt, favorable action thereon is earnestly solicited. If the Examiner believes that any points require additional consideration, the Examiner is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Frank R. Cottingham
Attorney/Agent for Applicants
Reg. No. 50,437

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
Tel. No. (973) 660-7660